Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT 2017

The Amended Protocol is Identified as:
Version 2.0, dated 16 August 2018
DAIDS Study ID #30070
IND #138,754

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2017 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed and all required approvals of this amendment must be obtained before initiating this study. Likewise, informed consent must be obtained for this study using site-specific informed consent forms that correspond to this amendment.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received before implementation of this amendment. Receipt of this notification will be confirmed as part of the site-specific study activation process for this study.

Please file this Summary of Changes, Version 2.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2017.
Summary and Rationale

The main purpose of this amendment is to implement protocol modifications recommended by the Division of AIDS responsible as the regulatory sponsor of the study relating to information about the study products that became available after protocol Version 1.0 was finalized, as well as increasing the flexibility in the timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1. This amendment also incorporates other modifications, clarifications and administrative edits to improve consistency across protocol sections.

Modifications incorporated into the protocol are summarized as follows:

- A recent report, based on a preliminary unplanned analysis of data from an observational surveillance study of birth outcomes conducted in Botswana, indicates a potential increased risk of neural tube defects (NTDs) associated with exposure to dolutegravir (DTG) at the time of conception. DTG is an integrase strand transfer inhibitor in the same class of pharmaceuticals as cabotegravir (CAB). The background section of the protocol has been updated to include a summary of the recently reported findings. The eligibility criteria, procedural section of the protocol has been updated to include the definition of a female of childbearing potential, that contraceptive counseling is required at all visits, and to specify the allowable contraceptive methods. The pregnancy management section of the protocol has also been updated to clarify that all pregnant female participants will be followed per the long-term safety and washout PK visit schedule, and the sample informed consents/assents of the protocol have been modified accordingly.

- The Other Objectives were modified to include describing the immunologic activity of the study agents by comparing their CD4 counts over the study period with their baseline value as well as characterize HIV-1 resistance in participants with virologic failure. The outcome measures and analyses sections of the protocol have been updated accordingly.

- The study design section of the protocol has been modified for increased flexibility in the timing of opening Cohort 2 to participants who have not previously enrolled to Cohort 1, and to clarify the visit flow for Cohort 1 Step 2 participants completing their Week 16 visit.

- The study eligibility criteria have been updated to clarify the allowable source documentation for inclusion criterion 4.1.7, the definition of an allowable blip in viral load for exclusion criteria 4.2.1, and that for exclusion criterion 4.2.2 the long-term safety follow-up and washout PK follow-up (LSFU) visits should also be included when assessing Cohort 1 participant eligibility for Cohort 2 Step 3. Step 2 and Step 4 eligibility criteria, Sections 4.3.2 and 4.4.2 have been clarified for consistency with Section 8.1.5 regarding Grade 2 ALT management at the Week 4a visit.

- The description of the recruitment and screening process has been updated to reflect expectations for limited data collection among potential participants who are screened but do not enroll in the study. This data collection will enable evaluation of reasons for non-enrollment and comparison of potential participants who are not enrolled with those who are enrolled. The description of baseline history data collection and corresponding sections of the sample informed consent and assent forms have also been updated.

- The study drug supply section of the protocol has been updated with revised storage instructions for oral CAB and CAB LA.
• The procedural sections of the protocol have been updated to provide further operational guidance with respect to the adherence assessment by pill count, the timing of the pre-dose PK draw at the Cohort 1 and Cohort 2 Week 4b visits, to clarify the Week 9 visit telephone contact may be conducted by voice or via text message, and to clarify the scheduling of the long-term safety and washout PK follow-up visits for Cohort 1 Step 2, Cohort 2 Step 4, and pregnant participants. The procedural sections of the protocol have also been updated to clarify the timing of conducting an early termination visit, and to improve consistency across protocol sections and clarify participant management for QTc prolongation. These sections have also been updated to clarify the number of aliquots required for Cohort 2 PK samples. CD4 counts have been added at specified study visits, and the Schedule of Evaluations updated to account for an increase in blood draw volumes. The requirement to consult the CMC prior to conducting an injection visit within the allowable window has been modified. Quantitative acceptability/tolerability assessments as well as conducting qualitative interviews (for selected participants) have been added to specified study visits, and the Schedule of Evaluations updated to account for these changes.

• The safety reporting section of the protocol has been updated to clarify the laboratory test values to be entered into eCRFs.

• The participant management sections of the protocol have been updated to clarify the general adverse event management for Grade 3 events assessed as not related to study product, and to provide additional guidance for assessing injection site reactions, CMC consultation for depression assessed as related to study product, and to improve consistency across protocol sections on participant management for QTc prolongation. These sections have also been updated to modify participant management for creatine kinase elevations, and to clarify participant management of a Grade 2 ALT occurring at the Week 4a visit.

• The statistical section of the protocol has been updated to modify the study design and analysis considerations to increase flexibility in the timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1. This section has also been updated to improve consistency across protocol sections on the review of safety data for the Cohort 1 interim analysis.

• The sample informed consent and assent forms have been updated to reflect the timing of the Week 4b visit and to reflect all other protocol modifications specified above. The sample informed consent and assent forms have also been corrected for grammar and typos.

• The protocol team and study site rosters have been updated to reflect current membership. References have been updated and other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity. The table of contents has been updated to reflect current protocol sections and page numbers and to include lists of tables and figures.

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**Implementation**

The changes in the protocol text and informed consent forms are summarized below, generally in order of first appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.
1. The amended protocol is identified as FINAL Version 2.0, dated 16 August 2018. The table of contents, abbreviation and acronym list, reference list, and protocol team and study site rosters have been updated. Additionally, the cover page was updated to include the IND number (#138,754).

2. In the Schema, Figures 1-4 have been updated to reflect the modified timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1. Figures 1 and 2 have also been simplified to improve readability of Cohort 1 and Cohort 2 design.

3. Section 1.2.1 was modified to add a new sub-section, Dolutegravir and Pregnancy, which summarizes the information involving the use of DTG in pregnancy from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study.

4. Figure titles were added to Figures 5, 6, and 7 in Section 1.2.3

5. Section 1.4.1 was clarified regarding the potential benefit for Cohort 1 participants of early access to Cohort 2, prior to study-naive Cohort 2 participants.

6. Section 2.5.2 was updated to add “immunologic” activity as part of the Other Objective. Section 2.5.6 was newly added to include a new Other Objective to describe HIV-1 resistance in participants experiencing virologic failure (Cohort 1 and Cohort 2).

7. Sections 3, 3.1, and 3.3 were updated to clarify the expected visit flow for Cohort 1 Step 2, Cohort 2 Step 4, and pregnant participants being followed per the long-term safety and washout PK (LSFU) schedule.

8. Section 3.1 was also updated to increase the flexibility in the timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1.

9. Inclusion criterion 4.1.7 was clarified to indicate that stable cART can be determined by the site IoR or designee, and based on participant or parent/guardian report and/or available medical records.

10. Inclusion criterion 4.1.15 was updated to specify contraceptive requirements for females of childbearing potential (from previously those self-reporting as sexually active). This criterion was also updated to incorporate the requirement of intention to delay pregnancy for a specified timeframe.

11. The definition of allowable unconfirmed blips in viral load was clarified in exclusion criterion 4.2.1.

12. Exclusion criterion 4.2.2 was clarified to include the LSFU visits when assessing Cohort 1 participants for Cohort 2 Step 3 eligibility.

13. Exclusion criterion 4.2.19 was clarified to also allow for parent/guardian report of lactation to be exclusionary.

14. Inclusion criteria 4.3.2 and 4.4.2 were clarified for consistency with Section 8.1.5.
15. Section 4.7.1 was updated to specify collection of limited demographic information and reasons for non-enrollment for potential participants who are screened but do not enroll in the study.

16. Sections 5.2.1. and 5.2.3 were updated with correct study product storage temperature ranges.

17. Section 5.6 was updated to clarify that herbal and traditional concomitant medications will not be captured in eCRFs, as consistent with Section 6.10.

18. Section 6.0 has been updated to clarify the location of information in sub-sections, as well as to reference the laboratory processing chart (LPC) for the number of required aliquots for the PK sample collections.

19. Section 6.1.1 has been retitled and reorganized to clarify the intention of scheduling study product injections within the various timeframes. Additionally, the requirement for CMC consultation to administer an injection within the allowable visit window was simplified to only require CMC notification; study staff are not required to receive a response from the CMC to administer an injection in specified scenarios. The following protocol sections were also modified to only require CMC notification prior to administering injectable study product within the allowable window: Sections 6.3.2, 6.3.7 through 6.3.9, and Sections 6.4.6 through 6.4.12.

20. Sections 6.3-6.5 have been updated to now require contraceptive counseling to be conducted at each study visit throughout Cohort 1 and Cohort 2 (including LSFU visits).

21. Sections 6.3 and 6.4 have also been updated to include an acceptability and tolerability assessment questionnaire, if indicated, at each study visit in addition to the following sections requiring acceptability and tolerability assessments: Sections 6.3.1, 6.3.4, 6.3.7, 6.3.9, 6.3.12, Sections 6.4.1, 6.4.4, 6.4.6, 6.4.8, 6.4.10, 6.4.12, Sections 6.5.1, and 6.5.5.

22. A blood collection for CD4 T lymphocyte (CD4) cell count evaluations have been added to Sections 6.3.1, 6.3.12, 6.4.8, 6.4.10, and 6.4.12. This added evaluation increases the blood collection volumes for these visits, and the Schedules of Evaluations have been updated accordingly.

23. Section 6.3.1, Cohort 1 Step 1 Entry visit, has been updated to clarify the required sequence of specified visit procedures. Reference to the IMPAACT 2017 Manual of Procedures (MOP) has been added regarding the timing of administering acceptability and tolerability questionnaires.

24. Section 6.3.2, Cohort 1 Step 1 Week 2 visit, has been updated to modify the recommended timing for participants to begin taking their oral study product, and increased the number of previous doses required for scheduling the Week 2 visit from two to three oral study product doses prior to the Week 2 visit. Guidance regarding when the Week 2 visit should be rescheduled, counseling participants to return all oral study product for the adherence assessment to be conducted, as well as providing adherence counseling has also been included.

25. Section 6.3.3, Cohort 1 Step 1 Week 4a visit, has been updated to include guidance on counseling participants to return all oral study product for the adherence assessment to be conducted; providing adherence counseling has also been included.
26. Section 6.3.4, Cohort 1 Week 4b Step 2 Entry visit, has been updated to modify the recommended timing for participants to begin taking their oral study product, and guidance regarding when the Week 4b visit should be rescheduled; increased flexibility in the timing of collecting the pre-dose PK blood collection has also been included. Providing adherence counseling has also been added to this visit.

27. Section 6.3.8, Cohort 1 Step 2 Week 9 visit, has been updated to clarify that the telephone contact may take place via a voice phone call or text message, in addition to specifying when a text message must be followed with a voice phone call for assessing any reported signs or symptoms.

28. Section 6.4.1, Cohort 2 Step 3 Entry visit, has been updated to clarify the required sequence of specified visit procedures. Reference to the IMPAACT 2017 Manual of Procedures (MOP) has been added regarding the timing of administering acceptability and tolerability questionnaires.

29. Section 6.4.2, Cohort 2 Step 3 Week 2 visit, has been updated to modify the recommended timing for participants to begin taking their oral study product, and increased the number of previous doses required for scheduling the Week 2 visit from two to three oral study product doses prior to the Week 2 visit. Guidance regarding when the Week 2 visit should be rescheduled, counseling participants to return all oral study product for the adherence assessment to be conducted, as well as providing adherence counseling has also been included.

30. Section 6.4.3, Cohort 2 Step 3 Week 4a visit, has been updated to include guidance on counseling participants to return all oral study product for the adherence assessment to be conducted; providing adherence counseling has also been included.

31. Section 6.4.4, Cohort 2 Week 4b Step 4 Entry visit, has been updated to modify the recommended timing for participants to begin taking their oral study product, and guidance regarding when the Week 4b visit should be rescheduled; increased flexibility in the timing of collecting the pre-dose PK blood collection has also been included. Providing adherence counseling has also been added to this visit.

32. Section 6.5 has been updated to clarify the intended scheduling of the long-term safety and washout PK follow-up (LSFU) visits, and entry points of specified participants into this visit schedule, including pregnant participants. The visit names have been modified to remove the specification of “post-last injection”. Additionally, this section has been updated to reference the LPC for the number of required aliquots for the PK sample collections.

33. Sections 6.5.1 through 6.5.5 have been updated to include that the qualitative phone interview may be conducted with selected participants during these visits.

34. Section 6.5.5 was updated to clarify the intended timing and target dates of conducting an Early Termination visit.

35. Section 6.9, Procedures for Continued Oral and Injectable Study Product Administration, was updated to include that, for females of childbearing potential, confirmation (per participant report) of allowable effective contraception is required prior to administering study product.

36. Section 6.10, Table 7, Documentation Requirements for Medical and Medication Histories, was updated to include collection of sex at birth.
37. Section 6.12, Performing an Electrocardiogram, was updated to clarify the intended timing of when a repeat triplicate ECG reading is required prior to Entry, and to clarify the intended trigger for a repeat triplicate during study follow-up visits (as consistent with Section 8.2).

38. Section 6.13, Pregnancy Testing and Contraceptive Counseling, has been modified to specify that all female participants of childbearing potential are required to use an allowable effective method of contraception to continue study product use. The definition of childbearing potential as well as a listing of allowed methods of contraception have been included. Guidance on counseling participants to delay pregnancy has been included. The requirement of confirming an allowable effective contraception prior to administering study product has also been added.

39. Section 6.14, Study Product Adherence Assessment and Adherence Counseling, was updated to clarify the intended purpose of the pill count assessment versus adherence counseling discussions, and how these visit procedures are to be used to inform the investigator’s determination of Step 2 (or Step 4) eligibility.

40. Section 6.15, Acceptability and Tolerability Assessments, has been updated to reference the IMPAACT 2017 MOP for the required timing of administering each assessment questionnaire. Additionally, language was added clarifying that an acceptability/tolerability assessment questionnaire will be required for any participant who prematurely permanently discontinues study product (oral or injectable study product) or study participation.

41. Section 7.2, Safety-Related Data Collection, was modified to simplify the laboratory test results to be entered into eCRFs.

42. Section 8.1, Management of Adverse Events, has been updated for grammatical errors.

43. Section 8.1.2, Injection Site Reactions (ISR), has been modified to add the definition of when an adverse event is considered an ISR.

44. Section 8.1.3, Creatine Kinase Elevation, has been modified to simplify the study product management and CMC consultation requirements.

45. Section 8.1.5, Elevations in ALT, Bilirubin, has been modified to increase consistency with participant and study product management of Grade 2 ALT elevations occurring at the Week 4a study visit (for either Cohort 1 or Cohort 2).

46. Section 8.1.9, Depression, Suicidal Ideation or Attempt, has been modified to simplify the study product management and CMC consultation requirements.

47. Section 8.2, Monitoring and Management of QTc Prolongation, has been updated to be consistent across protocol sections regarding the intended participant management.

48. Section 8.3, Management of Contraception and Pregnancy, has been updated to maintain consistency with Section 6.13. The requirement to obtain pregnancy outcomes has also been clarified.

49. Section 8.6, Deferring Study Product and Criteria for Temporary Hold of Study Product, has been simplified other relevant protocol sections referenced.
50. Section 8.7, Criteria for Premature Permanent Discontinuation of Study Product, has been updated to maintain consistency with other relevant protocol sections, including Section 6.5 and 6.5.5.

51. Section 9.2, Outcome Measures, and Section 9.6.4, Other Analyses, have been updated to newly include outcome measures and planned analyses relating to the newly added Other Objective in Section 2.5.6 (HIV resistance), as well as the revised Other Objective 2.5.2 (immunologic activity).

52. Section 9.5.1, Monitoring by the Protocol Team, and Section 9.5.2, Monitoring by the SMC, have been updated to modify the study design and analysis considerations to increase flexibility in the timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1. This section has also been updated to improve consistency across protocol sections on the intended review of safety data for the Cohort 1 interim analysis.

53. Sections 9.6.2, Primary Safety Analyses, and 9.6.3.2, Secondary Analyses, Safety, have been updated to improve consistency across protocol sections, per the outcome measures and study objectives, on the intended safety analyses.

54. Section 11.1, Sample Size and Selection Process, and Section 11.2, Qualitative Phone Interview Procedural Window, have been updated to include that selection of participants to take part in a single in-depth qualitative interview may occur after the participant has already entered the interview procedural window, and to add the LSFU visits (for both Cohort 1 and Cohort 2) to the interview procedural windows.

55. Section 12.1, Data Management Responsibilities, and Section 12.2, Essential and Source Documents and Access to Source Data, have been updated to clarify that the audio recordings of the qualitative interviews will be kept secure with the protocol interview team conducting the interviews.

56. Section 14.5, Potential Risks, was modified to add potential risk information involving the use of DTG in pregnancy from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study.

57. A reference has been added relating to the DTG and NTD findings.

58. Appendix I-A, Schedule of Evaluations for Cohort 1, was updated for the following:
   a. Acceptability/Tolerability assessment row: assessments were added as required at specified study visits, and if indicated at specified visits.
   b. CD4 count row: newly added with evaluations at specified study visits.
   c. Total maximum volume row: updated to account for increased blood volumes due to CD-4 testing.
   d. Footnote #3: newly added to clarify that an acceptability/tolerability assessment questionnaire is required for any participant who prematurely permanently discontinues study product (oral or injectable study product) or study participation.

59. Appendix I-B, Schedule of Evaluations for Cohort 2, was updated for the following:
   a. Acceptability/Tolerability assessment row: assessments were added as required at specified study visits, and if indicated at all other visits.
   b. CD4 count row: newly added with evaluations at specified study visits
c. Total maximum volume row: updated to account for increased blood volumes due to CD-4 testing
d. Footnote #2: newly added to clarify that an acceptability/tolerability assessment questionnaire is required for any participant who prematurely permanently discontinues study product (oral or injectable study product) or study participation.

60. Appendix I-C, Schedule of Evaluations for Long-Term Safety and Washout PK Follow-up (LSFU), was updated for the following:
   a. LSFU study visit names were modified to remove the specification of “post-last injection”.
   b. Acceptability/Tolerability assessment row: assessments were added as required at specified study visits.
   c. Qualitative Interview row: newly added to allow for selected participants to take part in an in-depth qualitative interview during the LSFU visits.
   d. Footnote #4: newly added to clarify that only a sub-set of participants will conduct the qualitative phone interview.
   e. Footnote #5: newly added to clarify that pregnancy testing will not be required for participants who are currently pregnant.

61. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, About the study, ViiV Healthcare was added to clarify the pharmaceutical support. This update was also included in Appendices II-B, III-A, and III-B.

62. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #5, was updated to include that all female participants of childbearing potential are required to use an allowable effective method of contraception to continue study product use, and intention to delay pregnancy. This includes allowing abstinence as an acceptable method of contraception in those reporting not being sexually active with reassessment of sexual activity at every study dispensation visit. The requirement of confirming an allowable effective contraception prior to administering study product has also been added, as well as clarification that pregnancy outcomes will be obtained even if occurring after study exit. This update was also included in Appendices II-B, III-A, III-B, and in Appendices IV-A and IV-B.

63. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #6, was updated to include limited data collection for potential participants who screen but do not enroll in the study. This update was also included in Appendices II-B, III-A, III-B, IV-A, and IV-B.

64. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #7, was updated to include contraceptive counseling and CD4 cell count blood sample collection. This update was also included in Appendices II-B, III-A, and III-B.

65. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #8, was updated to clarify the intended study design of the long-term safety and washout PK follow-up schedule. This update was also included in Appendices II-B, III-A, and III-B.

66. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Sections #9 and #10, were updated to clarify the timing of the Week 4b visit as occurring within Step 2 (or Step 4). This update was also included in Appendices II-B, III-A, and III-B.
67. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #11, was updated to include contraceptive counseling, acceptability/tolerability assessment questionnaires, and CD4 counts at specified visits. This update was also included in Appendices II-B, III-A, and III-B.

68. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #12, was updated to include additional details regarding the in-depth qualitative interviews. This update was also included in Appendices II-B, III-A, and III-B.

69. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #13, was updated to clarify the intended study design of the long-term safety and washout PK follow-up schedule. This update was also included in Appendices II-B, III-A, and III-B.

70. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #16, was updated to clarify the intended study design of the long-term safety and washout PK follow-up schedule, and to include contraceptive counseling. This update was also included in Appendices II-B, III-A, and III-B.

71. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #18, was updated to remove that pregnant participants would be discontinued from study participation. This update was also included in Appendices II-B, III-A, and III-B.

72. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Risks of the study, was updated to include potential risks during the long-term safety and washout PK follow-up visits. This update was also included in Appendices II-B, III-A, and III-B.

73. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #25, Possible effects on pregnancy or unborn babies, was updated include potential risk information involving the use of DTG in pregnancy from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study. This update was also included in Appendices II-B, III-A, and III-B.

74. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, What happens in the study, was updated to include that all female participants of childbearing potential are required to use an allowable effective method of contraception to continue study product use, and intention to delay pregnancy, as well as clarification that pregnancy outcomes will be obtained even if occurring after study exit. This updated was also included in Appendix IV-B.

75. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, First phase of the study, Second phase of the study, and Long-term follow-up safety phase of the study, were updated to clarify the timing of the Week 4b visit as occurring within Step 2 (or Step 4). This update was also included in Appendix IV-B.

76. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, Risks of the study, was updated to include potential risk information involving the use of DTG in pregnancy from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study. This update was also included in Appendix IV-B.
77. Appendix V-A, Section 1, Sample Size and Selection Process, and Section 2, Qualitative Phone Interview Procedural Window, have been updated to include that selection of parent/caregiver to take part in a single in-depth qualitative interview may occur after the parent/caregiver has already entered the interview procedural window, and to add the LSFU visits (for both Cohort 1 and Cohort 2) to the interview procedural windows.

78. Appendix V-A, Section 3, Recruitment Considerations, and Section 5, Eligibility Confirmation and Enrollment Process, have been updated to clarify that sites must follow their IRB/EC approved recruitment methods for approaching a potential parent/caregiver participant, and that eligibility criteria must be confirmed and source documented after obtaining informed consent.

79. Appendix V-A, Section 6, Scheduling and Conducting Phone Interviews, has been updated to clarify that scheduling of the interview may occur at any point with the intention to minimize the number of scheduled but uncompleted interviews. Parents/caregivers must be consented, confirmed as eligible, and enrolled prior to conducting the phone interview.

80. Appendix V-B, Section 6, Parent/Caregiver Phone Interview Sample Informed Consent Form, has been modified that audio recordings will not be deleted, and to include the LSFU visit window.

81. Appendix V-B, Section 6, Parent/Caregiver Phone Interview Sample Informed Consent Verbal Script, has been modified that audio recordings will not be deleted, and to include the LSFU visit window.